Claims:

1 (Currently amended): A time-temperature indicator device for monitoring the immunological risk status of a therapeutic protein drug;
said indicator being associated with said drug throughout the majority of the drug's storage life;
said indicator comprising;
a time-temperature integrator with means to integrate time and temperature, an indicator output means, and a time-temperature indication parameter setting means;
said indicator having at least one time-temperature indication parameter previously selected by:
monitoring chemical and structural changes in the therapeutic protein as a function of time and storage temperature;
determining which time and temperature conditions cause a certain percentage of said protein to undergo structural or chemical alterations;
said percentage being set at a predetermined immunological risk threshold wherein amounts above said threshold have an unacceptable risk of provoking an immunological reaction;
in which said therapeutic protein drug does not normally provoke an immunological reaction in the absence of said structural or chemical alterations, and in which said therapeutic protein drug is not a vaccine;
said structural alterations being selected from the group consisting of protein aggregation, denaturation, dimerization, oxidation, deamidation, disulfide exchange, proteolysis, peptide map change, creation of antigenic activity, creation of antibody epitopes, or destruction of antibody epitopes;
Ssaid immunological risk threshold being set at or below ten percent of the total quantity of said therapeutic protein;
in which said indicator output means output information pertaining to the immunological risk status of said therapeutic protein drug.

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2 (Currently amended): The time-temperature indicator device of claim 1, in which the indicator is a chemically based integrating time-temperature indicator with a visual display.

3 (Currently amended): The time-temperature indicator device of claim 1, in which the indictor is an electronic integrating time-temperature indicator with a visual display.

4 (Canceled):

5 (Currently amended): The time-temperature indicator device of claim 1, in which the indicator device is a unitized electronic time-temperature integrator that contains computational means, and a temperature measurement means:
wherein said indicator periodically samples the temperature and computes a function of temperature that is continually operative throughout the relevant temperature monitoring range of the indicator;
and wherein said function of temperature approximates the impact that the relevant temperature, for that period's length of time, has on alterations in the structure or chemistry of said therapeutic protein;
and wherein said computational ~~computing~~ means generate a running sum of said function of temperature over time;
and wherein said function of temperature resides with said unitized device;
and wherein the granularity of the function of temperature is small enough, and the frequency of time measurements is often enough, as to substantially approximate the impact of time and temperature on the alterations in the structure or chemistry of said therapeutic protein;
and in which said running sum is compared to a reference value, and the result of said comparison is used to generate an output signal indicative of the immunological risk status ~~fitness for use~~ of said therapeutic protein.

6 (Original): The time-temperature indicator device of claim 1, in which the device additionally monitors parameters selected from the group consisting of motion, vibration,

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light, or turbidity, and adjusts its immunological risk threshold depending upon said additional parameters.

7. An electronic time-temperature indicator device for monitoring the immunological risk status of a non-vaccine therapeutic protein drug:
said indicator being associated with said drug throughout the majority of the drug's storage life:
said indicator comprising:
a unitized electronic time-temperature integrator with means to integrate time and temperature, an indicator output means, and a time-temperature indication parameter setting means;
said indicator having at least one time-temperature indication parameter previously selected by:
monitoring chemical and structural changes in the therapeutic protein as a function of time and storage temperature:
determining which time and temperature conditions cause a certain percentage of said protein to undergo structural or chemical alterations;
said percentage being set at a predetermined immunological risk threshold wherein amounts above said threshold have an unacceptable risk of provoking an immunological reaction;
in which said therapeutic protein drug does not normally provoke an immunological reaction in the absence of said structural or chemical alterations;
said structural alterations being selected from the group consisting of protein aggregation, denaturation, dimerization, oxidation, deamidation, disulfide exchange, proteolysis, peptide map change, creation of antigenic activity, creation of antibody epitopes, or destruction of antibody epitopes;
said immunological risk threshold being set at or below ten percent of the total quantity of said therapeutic protein;
said indicator producing an output signal when said time-temperature indication parameters exceeds ~~a preset~~ said set limit-;

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in which said output signal outputs information pertaining to the immunological risk status of said therapeutic protein drug.

8 (Original): The device of claim 7, in which the output signal is selected from the group consisting of visual output signals, vibration signals, sonic signals, radiofrequency signals, electrical signals, or infra-red signals.

9 (Original): The device of claim 7, further containing means to enable the time-temperature indication parameters to be automatically programmed into the assembled device.

10 (Original): The device of claim 7, in which the time-temperature indication parameters are computed by a microprocessor, the device is continually powered throughout its use lifetime, and the power means is selected from the group consisting of battery, storage capacitor, thermal, photoelectric, AC power, or radio frequency energy.

11 (Original): The device of claim 7, in which the device additionally conveys information selected from the group consisting of thermal history statistics, percentage of remaining lifetime, identification codes, and therapeutic protein prescribing information.

12 (Currently amended): The time-temperature device of claim 7, in which the time-temperature device is incorporated into or interfaced with a therapeutic protein dispensing device, in which the time-temperature device signals if the therapeutic protein should be dispensed or not depending upon the acceptability of the material's thermal history.

13 (Currently amended): The time-temperature indicator device of claim 7, in which the time-temperature indicator device additionally monitors parameters selected from the group consisting of motion, vibration, light, or turbidity, and adjusts its immunological risk threshold depending upon said additional parameters.

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14 (Withdrawn): A method to determine the potential immunological risk of a therapeutic protein, said method comprising:
Constructing a pool of antibody or immune response genes representative of the genetic diversity of a target population:
Using said genetic pool to produce a panel of antibodies or immune response proteins directed against one or more representative samples of said therapeutic protein,
Using said panel to determine which epitopes are expressed on various preparations of said therapeutic proteins under various storage conditions:
said storage conditions representing at least different combinations of time and temperature storage parameters:
and determining what combinations of time and temperature storage parameters are associated with the formation of epitopes representative of immunogenic risk.

15 (Withdrawn): The method of claim 14, in which the panel of antibodies or immune response proteins is produced using methods selected from the group consisting of phage display, ribosome display, or lymphocyte antibody production methods.

16 (Withdrawn): The method of claim 14, used to optimize the structure, sequence, or chemical storage conditions of said therapeutic protein so as to minimize the chances of unwanted immunological activity with respect to said target population.

17 (Withdrawn): The method of claim 14, used as a method of manufacturing a drug compound, in which the method is used to optimize the drug structure to improve length of time and temperature that the drug may be stored before developing unwanted immunogenicity.

18 (Withdrawn): The method of claim 14, used to monitor the appearance of potentially immunogenic epitopes upon storage of a therapeutic protein.

19 (Withdrawn): The method of claim 14, used to determine optimal time-temperature storage conditions of a therapeutic protein.

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20 (New): The device of claim 1, in which the indicator output means is selected from the group consisting of visual output signals, vibration signals, sonic signals, radiofrequency signals, electrical signals, or infra-red signals.

21 (New): A method for setting a time-temperature indicator device for monitoring the immunological risk status of a therapeutic protein drug:
said indicator being associated with said drug throughout the majority of the drug's storage life, said method comprising:
providing a time-temperature integrator indicator with means to integrate time and temperature, an indicator output means, and a time-temperature indication parameter setting means;
said indicator having at least one time-temperature indication parameter selected by the immunological risk time-temperature data for said therapeutic protein drug, said data determined by the steps of:
monitoring chemical and structural changes in the therapeutic protein as a function of time and storage temperature:
determining which time and temperature conditions cause a certain percentage of said protein to undergo structural or chemical alterations:
said percentage being set at a predetermined immunological risk threshold wherein amounts above said threshold have an unacceptable risk of provoking an immunological reaction:
in which said therapeutic protein drug does not normally provoke an immunological reaction in the absence of said structural or chemical alterations, and in which said therapeutic protein drug is not a vaccine:
said structural alterations being selected from the group consisting of protein aggregation, denaturation, dimerization, oxidation, deamidation, disulfide exchange, proteolysis, peptide map change, creation of antigenic activity, creation of antibody epitopes, or destruction of antibody epitopes:
said immunological risk threshold being set at or below ten percent of the total quantity of said therapeutic protein:

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and setting said time-temperature indication parameter of said time-temperature integrator indicator with said immunological risk time-temperature data.

22 (New): A method for monitoring a therapeutic protein drug for immunological risk, said method comprising:
providing a time-temperature integrator indicator with means to integrate time and temperature, an indicator output means, and a time-temperature indication parameter setting means;
said indicator having at least one time-temperature indication parameter selected by the steps of:
monitoring chemical and structural changes in the therapeutic protein as a function of time and storage temperature;
determining which time and temperature conditions cause a certain percentage of said protein to undergo structural or chemical alterations;
said percentage being set at a predetermined immunological risk threshold wherein amounts above said threshold have an unacceptable risk of provoking an immunological reaction;
in which said therapeutic protein drug does not normally provoke an immunological reaction in the absence of said structural or chemical alterations, and in which said therapeutic protein drug is not a vaccine;
said structural alterations being selected from the group consisting of protein aggregation, denaturation, dimerization, oxidation, deamidation, disulfide exchange, proteolysis, peptide map change, creation of antigenic activity, creation of antibody epitopes, or destruction of antibody epitopes;
said immunological risk threshold being set at or below ten percent of the total quantity of said therapeutic protein;
setting said time-temperature indication parameter of said indicator with said immunological risk time-temperature data;
associating said immunological risk set indicator with said drug throughout the majority of the drug's storage life;

and monitoring the immunogical risk status of said therapeutic drug by observing the indicator output of said time-temperature integrator.

23 (New): The method of claim 22, in which the indicator output means is selected from the group consisting of visual output signals, vibration signals, sonic signals, radiofrequency signals, electrical signals, or infra-red signals.

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